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(54) PHARMACEUTICAL COMPOSITION CONTAINING A CLAVULANIC ACID DERIVATIVE

(71) We, BEECHAM GROUP LIMITED, of Beecham House, Great West Road, Brentford, Middlesex, a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a pharmaceutical composition comprising the crystalline sodium salt of clavulanic acid methyl ether.

British Patent Application No. 41897/75—02629/76—1900/76 (Serial No. 1,565,209) cognate discloses inter alia the sodium salt of the methyl ether of clavulanic acid. It has now been found that a crystalline sodium salt of clavulanic acid methyl ether obtained by crystallisation from a non-hydroxylic organic solvent such as ethyl acetate or acetone-diethyl ether mixtures is particularly suitable for use in the preparation of sterile pharmaceutical compositions adapted for administration by injection or infusion. The salt has the infra red spectrum substantially as shown in the Figure herein.

The present invention provides a pharmaceutical composition adapted for administration by injection or infusion which comprises the crystalline sodium salt of clavulanic acid methyl ether and a pharmaceutically acceptable carrier.

The composition of this invention may be used in the treatment of mammals including humans. These compositions have the advantage of being able to produce high tissue levels of the medicament after administration. Suitable indications for use include infections of the respiratory tract, the urinary tract and mastitis in cattle.

The composition of this invention will normally be in the form of a reconstitutable powder and will be sterile. Such forms may contain conventional pharmaceutically acceptable materials such as preservatives and will be presented in accordance with conventional pharmaceutical practice in the manner well understood by those skilled in the art of formulating antibiotics.

Unit dose forms according to this invention will normally contain from 50 mg to 500 mg of the crystalline salt of the clavulanic acid methyl ether and more suitably from 50 mg to 250 mg of this crystalline salt.

The composition of this invention may be administered 1—6 times a day or more usually 2—4 times a day. The normal daily dose of the ether is from 50 mg to 3000 mg and more usually from 100 mg to 1000 mg.

The composition of this invention may also comprise a penicillin or cephalosporin in the manner described in Application No. 41897/75—02629/76—19000/76 (Serial No. 1,565,209) cognate. Suitable penicillins include ampicillin, amoxycillin, carbenicillin and ticarcillin which are used in the form of a salt suitable for administration or infusion. The weight ratio of the crystalline sodium salt of clavulanic acid methyl ether to the penicillin or cephalosporin may be, for example, 10:1 to 1:3 and advantageously may be from 5:1 to 1:2, for example 3:1 to 1:1.

Particularly favoured compositions of this invention will contain from 150 mg to 1000 mg of a salt suitable for administration or infusion of amoxycillin or a salt suitable for administration or infusion of ampicillin and from 50 mg to 500 mg of the crystalline sodium salt of clavulanic acid methyl ether. More suitably the composition will contain from 200 mg to 500 mg of the salt suitable for administration or infusion of amoxycillin or salt suitable for administration or infusion of ampicillin and from 50 mg to 250 mg of

the crystalline sodium salt of clavulanic acid methyl ether.

The following Examples illustrate the preparation of the crystalline salt.

Example 1

Amorphous sodium clavulanyl methyl ether (500 mg) was added to ethyl acetate (50 ml) and the mixture gently boiled for 5 minutes. The solution was filtered hot and the filtrate allowed to cool to room temperature when crystals appeared. When crystallisation appeared complete the crystals were filtered off and dried in dry air to yield the desired crystalline sodium clavulanyl methyl ether.

Example 2

Amorphous sodium clavulanyl ethyl ether (100 mg) was dissolved in hot acetone (4 ml). The solution was filtered and the filtrate allowed to cool to room temperature. To this was added ether (about 20 ml) dropwise until crystals appeared. The suspension was boiled to dissolve the crystals and then allowed to cool. After cooling in an ice bath and scratching for a few minutes the desired crystalline material formed and was collected by filtration.

The infra-red spectrum of the fine crystals is shown in the Figure herewith (KBr disc, 0.4% w/w in 300 mg disc).

Example 3

Amorphous sodium clavulanyl methyl ether (100 mg) was heated to 70°C in ethyl acetate (10 ml) for several minutes. The resulting clear solution was cooled slowly and maintained at 20°C. Small spots of oil appeared, from which grew clusters of crystals.

The crystals were filtered off, washed with a little ethyl acetate, and dried in air for 20 minutes, to yield the desired crystalline sodium clavulanyl methyl ether.

Preparation 1

The amorphous salt used in Examples 1, 2 and 3 may be prepared as follows:

Benzyl clavulanate (300 mg) was dissolved in dry methylene dichloride (25 ml) and cooled to 0°C. Boron trifluoride etherate (5 drops) was added at 0°C, followed by a solution of diazomethane in ether. The reaction mixture was stirred at 0°C for one hour and washed with 3 sodium bicarbonate solution (2 × 25 ml). The organic phase was dried over magnesium sulphate and evaporated; chromatographic purification gave benzyl clavulanyl ether (66 mg). A portion of this ether (30 mg) was dissolved in tetrahydrofuran (3 ml) and 10% palladium on charcoal (10 mg) added. The solution was hydrogenated at ambient temperature and pressure for 15 minutes, filtered and sodium bicarbonate (8.4 mg) in 0.5 ml water was added. The solvent was evaporated to yield the sodium clavulanyl methyl ether as an amorphous solid after trituration with ether (15 mg of product).

WHAT WE CLAIM IS:—

1. A pharmaceutical composition adapted for administration by injection or infusion which comprises the crystalline sodium salt of clavulanic acid methyl ether and a pharmaceutically acceptable carrier.
2. A composition as claimed in claim 1 in the form of a reconstitutable powder which is sterile.
3. A composition as claimed in claims 1 or 2 in the form of a unit dose containing 50 mg to 500 mg of the crystalline sodium salt of clavulanic acid methyl ether.
4. A composition as claimed in claim 3 which comprises 50 mg to 250 mg of the crystalline sodium salt of clavulanic acid methyl ether.
5. A composition as claimed in any of claims 1 to 3 which also comprises a penicillin or cephalosporin.
6. A composition as claimed in claim 5 wherein the weight ratio of crystalline sodium salt of clavulanic acid methyl ether to penicillin or cephalosporin is from 5:1 to 1:2.
7. A composition as claimed in claim 5 wherein the weight ratio is 3:1 to 1:1.
8. A composition as claimed in any of claims 1 to 3 which comprises 150 mg to 1000 mg of a salt suitable for administration or infusion of amoxycillin or a salt suitable for administration or infusion of ampicillin and from 50 mg to 500 mg of the crystalline sodium salt of clavulanic acid methyl ether.
9. A composition as claimed in any of claims 1 to 3 which comprises from 200 mg to 500 mg of a salt suitable for administration or infusion of amoxycillin or a salt suitable for administration or infusion of ampicillin and from 50 mg to 250 mg of the crystalline sodium salt of the clavulanic acid methyl ether.

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COMPLETE SPECIFICATION

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